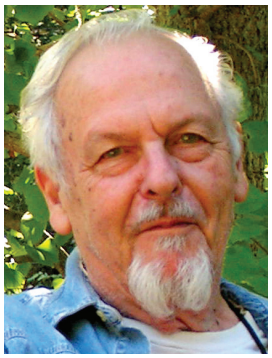
Still No Cure for Alzheimer's Disease



James Duke, PhD

James Duke served the US Department of Agriculture for over 30 years of his distinguished career. Before retiring, he developed the online Dr. Duke's Phytochemical and Ethnobotanical Databases. It is one of the most frequently consulted areas of the USDA website. He grows hundreds of plants on his six-acre Green Farmacy Garden with his wife, Peggy. Since retiring from the USDA, Dr. Duke served for five years as Senior Science Advisor to Nature's Herbs and with allherb.com. Since 2001, he has been a distinguished herbal lecturer at Tai Sophia Healing Institute (now Maryland University of Integrative Health). He has written over 30 books on medicinal plants.
www.phytochem.nal.usda.gov/phytochem/search
www.thegreenfarmacygarden.com/

In the beginning, there were Acetylcholinesterase Inhibitors (AChEIs), and though nearly useless, they prevailed for two decades backed by Big Pharma and approved by the FDA. By 1994, reductionists like me took the bait and started looking for herbal alternatives to tacrine (Cognex), assuming that inhibition of the cholinesterase enzyme would prevent the breakdown of acetylcholine, the mental messenger in the brain.

That summarizes the first two decades of the failed cholinergic hypothesis that drove most anti-Alzheimer's research. I hoped that then-FDA Commissioner David Kessler was right when he said, "It is not a cure, but it provides some relief for patients and their families." Early research led optimists to say it might help some 12% of Alzheimer's disease (AD) patients.

Eager beaver reductionist that I am, I went to my USDA public domain database seeking herbs with anti-acetylcholinesterase actions. Even though I had been gradually inputting the data since 1977, I was poetically pleased when my computer told me that rosemary (*Rosmarinus officinalis*), Shakespeare's herb of remembrance, was one of my best sources of AChEI phytochemicals.

Now, in early 2016, my database contains 165 phytochemical AChEIs. Rosemary is still a leading source, with at least two dozen AChEIs (alpha-pinene, alpha-terpinene, alpha-terpineol, alpha-tocopherol, carvacrol, carvone, delta-3-carene, d-limonene, elemol, eugenol, ferulic acid, gamma-terpinene, isopulegol, limonene, linalool, luteolin, p-cymene, piperitenone, quercetin, sabinene, sinapic acid, terpinen-4-ol, thymol, and trans-anethole). Ditto for oregano (*Origanum vulgare*) and its 26 AChEI compounds. More than half of those are aromatic phytochemicals that can cross the blood-brain barrier, which leads me to encourage anti-AD clinical trials for several promising members of the mint family as well.

> WASHINGTON, September 9, 1993 – Tacrine, the first drug shown to have any effect on the devastating symptoms of Alzheimer's disease, was approved today by the Food and Drug Administration.
>
> (New York Times)

In 1994 I wagered, and in 2016 I still believe, that rosemary is all-around better for AD than tacrine (and that's not saying much). Our database finds 26 AChEIs in oregano, 16 in licorice (*Glycyrrhiza glabra*), 15 in sage (*Salvia officinalis*), 9 in turmeric (*Curcuma longa*), 6 in ginkgo (*Ginkgo biloba*), 5 in stinging nettle (*Urtica dioica*), and 4 in walnut (*Juglans* spp.).

Rosmarinus officinalis (rosemary)

Henriette Kress
www.henriettes-herb.com

From the Acetylcholine Hypothesis to the Amyloid-Beta Hypothesis

Tacrine was withdrawn in 2013 as relatively ineffective and with many side effects (tabulated in Google). Noting amyloid beta plaque in the brains of deceased AD patients, AD-ologists graduated to the amyloid beta plaque hypothesis. Science, if not Big Pharma and the FDA, now recognizes the ineffectiveness of AChEIs, like FDA-approved tacrine (Cognex) and donepezil (Aricept) in treating AD.

Amyloid-Beta-Inhibitors

By January 2016, our database had around 30 herbal species and more than 100 chemicals reported to block amyloid beta plaque, again including Shakespeare's herb of remembrance, rosemary, and, perhaps ironically, *Cannabis*. A synthetic cannabinoid, Hebrew University 210 (HU-210), is reportedly much more potent than tetrahydrocannabinol (THC) and prevents both the inflammation caused by amyloid beta proteins in AD and the cognitive impairment caused by the over-activation of microglia. In rats, cannabinoids prevent neurotoxicity induced by over-active microglia.

Here is a short list of spices and foods reported to help prevent amyloid beta plaque accumulation or to contain anti-plaque phytochemicals: celery, chickpea, chocolate, cinnamon, citrus, coconut, garlic, ginger, marjoram, noni, onion, olive, pomegranate, sage, sesame, and turmeric (from my proprietary database). None are approved as treatments for AD or mild cognitive impairment (MCI). Perhaps they can help, perhaps not. They have a lot of useful side effects (i.e., beneficial off-target activities).

From the database of herbs, our compilation finds 10 amyloid-beta-inhibitors in ginkgo, 8 in rosemary, 7 in oregano, 6 in sage, 5 in walnut, 4 in licorice, 3 in barberry (*Berberi*s spp.), 3 in stinging nettle, and 3 in turmeric. As opposed to the aromatic anti-cholinesterases, many of the anti-amyloid phytochemicals are NOT aromatic volatiles.

For example, consider berberine, an alkaloid isolated from *Berberis*, *Mahonia*, and other yellow-rooted species. In 2012, Hong Kong scientists working with a mouse model reported that berberine at oral doses of 25 mg/kg/day and 100 mg/kg/day was memorigenic and reduced amyloid plaque. We have several berberine-containing medicinal herbs in the Green Farmacy Garden. Several of the berberine-related alkaloids also reportedly have anti-AD activities: berberine, coptisine, groenlandicine, jatrorrhizine, and palmatine.

Other Anti-Amyloid Compounds

We have more than 30 anti-amyloid or anti-amyloid-plaque phytochemicals in the database as of January 2016. Many authors, even I, equate anti-amyloid with the above amyloid-beta-inhibitors, and both activities seem to reduce the potential for severe AD. Some of the more common anti-amyloid compounds reported (with suggested experimental dosage levels where available) are: apigenin, baicalein, baicalin, beta-sitosterol, cannabidiol (2.5-10 mg/kg ipr), catechin (50 uM), curcumin (0.5-10 ug/ml), demethoxycurcumin (0.5-10 ug/ml), melatonin, naringenin, quercetin, resveratrol (25-50 um), shogaol (4.5-81 um), and tetrahydrocannabinol.

The curcuminoids and shogaols make turmeric look like a promising anti-amyloid agent. Some anti-amyloid endocannabinoids (i.e., within the human) and exocannabinoids (i.e., from plants) make *Cannabis* spp. worthy of serious investigation. So far, my database has 8 anti-amyloid compounds for *Cannabis*, 5 for turmeric, 3 for licorice, 2 for oregano, 1 for walnut, and 1 for sage.

Anti-AGE Compounds

Advanced Glycation End Products (AGEs) are involved in a number of chronic inflammatory problems in degenerative diseases, including diabetic complications, atherosclerosis, AD, and inflammatory arthritis. Chinese scientists noted increased levels of AGEs in brains of AD patients. AGEs can induce an up-regulation of amyloid-beta production, inflammation, and oxidative stress (PubMed ID 26738988).

As of January 2016, there are 130 natural anti-AGE phytochemicals in my database. Some familiar anti-AGE compounds (with suggested experimental dosage levels) are: amentoflavone (50 uM), apigenin (~10 ug/ml), (+)-catechin (5.6 uM), diosmetin (~10 ug/ml), limonene (50 uM), obtusifolin (29 uM), scopoletin (~3 uM), and silymarin (~10 ug/ml). So far, we have 10 anti-AGE phytochemicals for ginkgo, 9 for *Cannabis*, 8 for nettle, 8 for rosemary, 7 for barberry, 7 for licorice, 7 for oregano, 4 for turmeric, and 4 for walnut. Many natural anti-AGE herbals are free of undesirable side effects (PMID 26293545).

Anti-Amnesia Compounds

"Amnesia" is sometimes used as a euphemism for AD in the literature, along with "dementia" and "MCI." If the authors used these buzzwords (or "Alzheimer's"), that's what is entered into my database. As of January 2016, there were 41 "anti-amnesia" compounds in my database: 3 for oregano, 3 for licorice, 3 for *Cannabis*, 2 for sage, 2 for rosemary, 2 for barberry, 1 for walnut, 1 for stinging nettle, and 1 for ginkgo.

Beta-Secretase-Inhibitors and BACE-1-Inhibitors

Beta-secretase-1 (BACE-1) is also known as beta-site amyloid precursor protein cleaving enzyme 1. Two sequential cleavages of the amyloid precursor protein are required for the formation of amyloid-beta plaque in AD, so inhibiting this cleaving enzyme could be helpful in preventing or slowing AD. I have learned that the buzzword BACE-1-Inhibitor includes alpha, beta, and gamma secretase inhibitors.

I was surprised how many BACE-1-Inhibitors or Beta-Secretase-Inhibitors there are: >1000 PubMed citations on Beta-Secretase-Inhibitors and >500 citations on BACE-1-Inhibitors. BACE-1-Inhibitors (with probable IC50 effectiveness levels) have been reported from *Abronia nana* (abronione-A, IC50≈62 uM; boeravinone-D, IC50≈5 uM; mirabijalone-D, IC50≈4 uM, PMID 24835197), *Aloe arborescens* (aloenin-A,(E)-2-acetonyl-8-(2'-O-feruloxyl)-beta-D-glucopyranosyl-7-methoxy-5-methyl-chromone, 7-O-methylaloeresin-A, barbaloin-A, PMID 17184120), *Alpinia officinarum* (galangin, PMID 25779965), *Anemarrhena* spp. (Timosaponin II, PMID 23082924), *Betula platyphylla* (PMID 25301235), *Buxus macowanii* (Nb-demethylpapillotrienine, 31-hydroxybuxatrienone, PMID 25528196), *Caragana indica* (alpha-viniferin, PMID 26407945), *Curcuma longa* (bisdemethoxycurcumin, IC50=17 uM, PMID 24597901), *Gelsemium sempervirens* (IC50≈16 ug/ml, PMID 25459447), *Geranium thunbergi*i (corilagin, geraniin, PMID 23877922), *Melia toosendan* (PMID 24566006), *Panax ginseng* (ginsenosides CK, F1, Rh1, and Rh2, PMID 23816176), *Pistacia integerrima* (pistagrenic acid, IC50≈350 nM, PMID 25588845), *Prunus salicina*,

Mahonia aquifolium (Oregon-grape, hollyleaved barberry). The yellow roots are used medicinally.

H. Zell (CC BY-SA 3.0)

Cannabis sativa
(hemp, marijuana) flower

Bokske (CC BY-SA 3.0)

Rosmarinus officinalis (carnosic acid; PMID 23257508, PMID 24295810), *Trifolium pratense* (pratensin, PMID 25665942), *Tripterygium wilfordii* (tripfordin-B1, PMID 24900984; triptolide, PMID 25481013), and a number of other plants. [Note: IC50 is a measure of how much of a particular drug or substance is needed to inhibit a given biological process by half.]

The most recent citations on the Beta-Secretase-Inhibitors reintroduced me to oligonol, a low-molecular-weight polyphenol derived from lychee fruit (*Litchi chinensis*) extract. It contains catechin-type monomers and oligomers of proanthocyanidins. It may slow or prevent AD by inhibiting acetylcholinesterase (AChE, IC≈4 ug/ml), butyrylcholinesterase (BChE, IC50≈2 ug/ml), and BACE-1 (IC50≈130 ug/ml).

Interestingly, a 2014 study listed 12 drug companies working on BACE-1-Inhibitors (I presume synthetic and probably with many side effects if unknown to your genes). As almost always, I can find a much longer list of natural BACE-1-Inhibitors from common food plants, which are probably better known to your genes than synthetic BACE-1-Inhibitors and hence safer.

Butyrylcholinesterase-Inhibitor (BChEI) Compounds

The BChEIs, like the AChEIs, preserve the cerebral butyrylcholinergic messengers by inhibiting enzymes that break them down. Both BChEIs and AChEIs are screened for during the search for choline preservers. Some of the better known of the 16 BChEIs in my database (with suggested experimental dosage levels) include anethole (75 ug/ml), berberine, carvone (~1 mg/ml), genistein (~1 mg/ml), and silybin (~1 mg/ml). Then there is the more dangerous galanthamine (12,590 nm/l) and huperzine-A (58,895 nm/l), and the very dangerous physostigmine (1,259 nm/l). So far, our database lists 5 BChEI compounds for *Cannabis*, 3 for rosemary, 3 for oregano, 2 for sage, 2 for licorice, 1 for turmeric, and 1 for barberry.

Anti-Dementia Compounds

By January 2016, we have more than 165 anti-dementia entries in our database, "dementia" being often used as a less derogatory term for AD or for pre-AD conditions. Some authors use these terms interchangeably, while others may view them as slightly different, but the database has almost as many phytochemicals labeled for dementia (186) as for AD (205). Seeing gingerol, paradol, and shogaol as anti-dementia compounds makes me want to improve and invigorate my old "Creme Dementia" formula with some piquant slivers of ginger, and my "Alzheimaretto" with some of the anti-AD mints which grow so well, almost like weeds...all in the Green Farmacy Garden.

For anti-dementia compounds in herbs, our database lists 20 in *Cannabis*, 19 in oregano, 16 in sage, 16 in ginkgo, 15 in walnut, 15 in rosemary, 15 in licorice, 14 in turmeric, and 9 in barberry. In January 2016, the Cannabis Phytochemicals Activities Database (CPAD) lists 22 anti-dementia compounds: two are endocannabinoids occurring in humans (2-arachidonoylglycerol, palmitoylethanolamide), two may be unique to *Cannabis* (cannabidiol, tetrahydrocannabinol), and the others are much more widely distributed in the plant kingdom (alpha-linolenic-acid, anethole, apigenin, ascorbic-acid, choline, ferulic acid, flavonoids, lecithin, luteolin, niacin, phosphatidylcholine, p-hydroxybenzoic acid, quercetin, thiamin, trigonelline, tryptophan, zeatin, and zinc).

Anti-AD Activity of Natural Compounds	# Compounds in *Cannabis*	# Compounds in Phytochemical Database
Amyloid-Beta-Inhibitor	16	124
Anti-amyloid	8	31
Anti-acetylcholinesterase (AChEI)	34	165
Anti-AGE	9	130
Anti-amnesic	3	41
Beta-Secretase-Inhibitor / BACE-1-Inhibitor	0	13
Anti-butyrylcholinesterase (BChEI)	5	16
Anti-dementia	20	186
Anti-excitotoxic	3	25
Anti-glutamate	4	13
Anti-tau	0	11
Cholinergic	6	45
MCI-Inhibitor	8	14
Memorigenic	6	85
Microglia-Inhibitor	0	5
Neurogenic	4	37
Neuroprotective	31	294
Nootropic	0	10
Herbistatin	12	42
Hypocholesterolemic	35	248
Notch-1-Signal-Enhancer	0	1
SIRT-Activator	3	10
	217	**1556**

Number of compounds with anti-AD activity in *Cannabis* and in the overall Phytochemical Database

Phytochemical Database (updated), accessed January 2016

Corrected to discount endocannabinoids, which occur in humans, not *Cannabis*

Anti-Excitotoxic Compounds

Excitotoxicity is the pathological process by which nerve cells are damaged or killed by excessive stimulation of naturally occurring neurotransmitters, such as glutamate and similar substances. As of early 2016, our database lists anti-excitotoxic compounds as 4 in licorice, 3 in ginkgo, 3 in *Cannabis*, 2 in walnut, 2 in turmeric, 2 in oregano, 2 in nettle, 2 in barberry, 1 in sage, and 1 in rosemary.

Glutamate is one of the major excitotoxins. A 2014 study with AD patients concludes, "Cholinesterase inhibitors and memantine [glutamate-blocking drug] are able to stabilize or slow decline in cognition, function, behavior, and global change" (PMID 24662102). The rather ubiquitous beta-sitosterol is also cited as an anti-glutamate compound.

Anti-Tau Compounds

The hypotheses about possible help for AD now seem to move back and forth from anti-amyloid compounds to anti-tau compounds. Like amyloid-beta plaque, tangles of defective tau proteins are found accumulated in the brains of AD patients and in more than 15 other neurodegenerative diseases. So far, we have only myricetin from ginkgo reported for anti-tau compounds in our database.

From PubMed, we see that three phytochemicals in common bayberry (myricanol, myricetin, myricetrin) can target tau turnover in AD. Myricanol may be of interest in AD drug development (PMID 21141876). In addition, oleocanthal, a component of olive oil, has been linked to reduced risk of Alzheimer's disease characterized by accumulation of ß-amyloid and tau proteins in the brain (PMID 23414128). Olive's hydroxytyrosol, oleuropein, and oleuropein aglycone can inhibit tau fibrillization at uM concentrations (PMID 21333710). If all else was failing, I might try steeping bayberry leaves in olive oil as a "food farmacy" effort, hoping they might interact with my endocannabinoids to help arrest the development of AD.

Memory-Enhancing Nootropics

I once thought "nootropic" was a rare word. Even today, I only have 10 nootropic phytochemicals listed in my database. But a PubMed search yielded 357 citations for nootropic compounds. Most researchers seem to define nootropic as memorigenic. Some seem to take a leap of faith in suggesting that nootropics, especially synthetics, might be useful for anti-AD or anti-amnesia actions. I'll avoid that leap of faith myself.

Nevertheless, among the nootropic herbs listed in the PubMed search are: *Abelmoschus esculentus* (PMID 25401145), *Achyranthes aspera* (PMID 26408046), *Alfredia cernua* (piracetam, PMID 21240347), *Alstonia scholaris* (PMID 19317351), *Andrographis paniculata* (PMID 22771592), *Argyreia speciosa* (PMID 22228958), *Asparagus racemosus* (PMID 21843599), *Bacopa monnieri* (PMID 19903380), *Capparis zeylanica* (PMID 22261859), *Celastrus paniculatus* (seed, PMID 20645820), *Centella asiatica* (PMID 22408313), *Clitoria ternatea* (PMID 24459404), *Convolvulus pluricaulis* (PMID 21846173), *Curcuma longa* (curcumin, PMID 22211188), *Cyperus rotundus* (PMID 26297840), *Desmodium* spp. (PMID 22004895), *Eclipta prostrata* (PMID 20851313), *Evolvulus alsinoides* (PMID 21846173), *Fumaria indica* (PMID 24696581), *Ginkgo biloba* (PMID 17480002; piracetam, PMID 23326356), *Glycine max* (isoflavones, PMID 22211188), *Hypericum perforatum*, (hyperforin, PMID 20836158; quercetin, PMID 23469842), *Juglans regia* (PMID 22048906), *Malus pumila* (phloretin, PMID 26071678), *Melissa officinalis* (terpenes, PMID 22211188), *Moringa oleifera* (PMID 24454988), *Nardostachys jatamansi* (PMID 21154640), *Nicotiana tabacum* (nicotine, PMID 22211188), *Ocimum sanctum* (PMID 16480180), *Oryza sativa* (bran oil, PMID 261399230), *Panax* spp. (terpenes, PMID 19140520, PMID 22211188), *Pedicularis* spp. (PMID 25242078), *Polygala tenuifolia* (tenuigenin, PMID 26220627), *Prosopis cineraria* (PMID 22906223), *Prunus dulcis* (PMID 23588464), *Ptychopetalum olacoides* (PMID 20833520), *Pueraria tuberosa* (PMID 18814488), *Rhodiola rosea* (PMID 20378318), *Rubia cordifolia* (PMID 17176672), *Salvia officinalis* (terpenes, PMID 22211188), *Tabernaemontana divaricata* (PMID 20435125), *Valeriana officinalis* (terpenes, PMID 22211188), *Vetiveria zizanioides* (PMID 26604550), *Vitis vinifera* (resveratrol, PMID 22211188), and *Withania*

somnifera (PMID 26361721). Among nootropic compounds listed are: caffeine (PMID 22211188), curcumin (PMID 22211188), epigallocatechin-3-gallate (PMID 22211188), isoflavones (PMID 22211188), nicotine (PMID 22211188), resveratrol (PMID 22211188), tenuigenin (PMID 22179853), and terpenes (PMID 22211188).

Synergic Food Farmacy?

Synthetic Silver Bullets,
Failed All these Years,
The Futile Alzheimeran Trail of Tears.
Am I dreaming? It seems to me
Answers await in synergy,
In safe nat'ral food farmacy.

What's it all to you and me?
Me and Peggy you see!
May have early AD!
And tho she don't know it,
I'm trying to slow it,
But it's already nibbling on me.

~ Anonymous poet (2016)

Conclusions

This reverie is not unique to me! In 2014 Australian scientists said, "...plant secondary metabolites have...antioxidant, anti-inflammatory, anti-amyloidogenic, neuroprotective, and cognition-enhancing effects...catechins/proanthocyanidins from green tea, curcumin from turmeric, extracts enriched in bacosides from Brahmi (*Bacopa monnieri*), flavone glycosides from *Ginkgo biloba*, and omega-3 polyunsaturated fatty acids. They...counteract one pathophysiological aspect of AD...but also ameliorate several of the above mentioned pathologies...[I] ncreased consumption of these compounds might lead to a safe strategy to delay the onset of AD" (PMID 25230232).

For example, a 2014 meta-analysis concluded that ginkgo may help stabilize AD patients with cognitive symptoms, but cannot prevent the neurodegenerative progression of the disease (PMID 24871648). In Europe, the benefit of treatment with the *Ginkgo biloba* extract EGb 761R (240mg/day) corresponds to a delay in AD deterioration by 22.3 months compared to placebo. Overall net savings with EGb 761R treatment ranged from €3,692 to €29,577, mainly driven by the delay of nearly two years in progression towards higher costs of home health care. In a tentative cost comparison, cholinesterase inhibitors required higher expenses to achieve similar treatment success (PMID 23292640).

In 2014, Iranian scientists clinically compared synthetic memantine (20mg/day/12 months) with saffron extract (30mg/day/12months) in patients with moderate to severe Alzheimer's disease. They found no significant differences in results or adverse events, concluding, "...1-year administration of saffron extract capsules showed to be comparable with memantine in reducing cognitive decline in patients with moderate to severe AD" (PMID 25163440).

Spanish scientists, in 2014, looked at diet, cognition, and Alzheimer's, and suggested a protective role for certain nutrients, such as omega-3 fatty acids, antioxidants, B vitamins, and overall dietary pattern (i.e., the Mediterranean diet); however, data from randomized controlled trials do not show a consistent effect (PMID 23892520). Epidemiology indicates a higher risk of cognitive decline in people in the lower quartile of omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs: DHA and EPA) intake or blood levels, but these populations have not been specifically targeted by randomized clinical trials (PMID 23459977). There is no convincing evidence that vitamin E is of benefit in the treatment of AD or MCI. Future trials assessing vitamin E treatment in AD should not be restricted to alpha-tocopherol (PMID 23152215).

In a 2012 study, British scientists recapitulated some of the more promising ethnobotanicals for AD – plants that had been clinically studied with dementia patients (e.g.,

Ginkgo biloba (ginkgo, maidenhair tree) leaves.

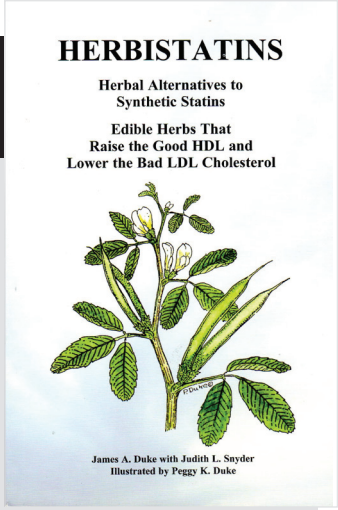
Juan Carlos López Almansa (CC BY-SA 2.0)

Crocus sativus, *Ginkgo biloba*, *Salvia* spp.) and plants showing relevant mechanistic effects for AD (e.g., *Bacopa monnieri*, *Centella asiatica*, *Ptychopetalum olacoides*) (PMID 22329652). A 2011 Brazilian study discussed 16 plants as potential sources of active extracts which they considered potentially useful for AD, some edible, some medicinal, some poisonous: *Celastrus paniculatus*, *Centella asiatica*, *Coptis chinensis*, *Crocus sativus*, *Curcuma longa*, *Evodia rutaecarpa*, *Galanthus nivalis*, *Ginkgo biloba*, *Huperzia serrata*, *Lycoris radiata*, *Magnolia officinalis*, *Panax* spp., *Picrorhiza kurroa*, *Polygala tenuifolia*, *Salvia lavandulaefolia*, *Salvia miltiorrhiza*, *Sanguisorba officinalis*, and *Veratrum grandiflorum* (PMID 20874701).

I strongly agree with Italian scientists, Russo et al. (2013): "It may be unlikely that AD may be mitigated by a drug acting on a single specific target...Alzheimer's disease is extremely complex and heterogeneous" (PMID 23410167). If we are still failing in the prevention and treatment of AD with synthetic silver bullets, we should not despair. Synthetics can do more harm than good.

It's time to explore potential natural shotgun pellets such as beta-amyloid-inhibitors, AChEIs, anti-AGEs, anti-amnesics, BChEIs, anti-dementias, anti-depressants, anti-excitotoxics, anti-microglials, anti-tauropathics, Beta-Secretase-Inhibitors, BACE-1-Inhibitors, cholinergics, herbistatins, hypocholesterolemics, MCI-inhibitors, memorigenics, neurogenics, neuroprotectives, nootropics, Notch-1-Signal-Enhancers, and SIRT-Activators. Most such herbs and natural compounds are worthy of consideration, and more meritorious and safer than their synthetic "equivalents," too many of which have been unloaded on us by Big Pharma and too readily approved by the FDA

ADDENDUM: "Herbistatins" and Statins in Alzheimer's Disease



In 2013, I published a little book with my long-time research associate, Judi duCellier Snyder, and illustrated by my wife Peggy K. Duke. The book is called, *Herbistatins – Herbal Alternatives to Synthetic Statins – Edible Herbs that Raise the Good HDL and Lower the Bad LDL Cholesterol.* On the back cover, I list 50 of a growing list of healthy herbistatins that never killed anyone. I challenge you to say how many Americans have been killed by synthetic statins, many of which have already been taken off the market by the same FDA that approved them.

I don't think the FDA will withdraw the following health-food herbistatins, nor do I think they will approve them for lowering cholesterol:

1. Almond,
2. Avocado,
3. Beet
4. Black beans
5. Black cumin
6. Black pepper
7. Black rice
8. Broccoli
9. Calabash gourd
10. Carob
11. Chickpea
12. Chocolate
13. Cinnamon
14. Coconut
15. Coriander
16. Cumin
17. Curry, leaf
18. Fenugreek
19. Flax
20. Garlic
21. Ginger
22. Grape
23. Grapefruit
24. Green tea
25. Horseradish tre
26. Kale
27. Lentils
28. Licorice
29. Mustard oil
30. Oat
31. Oil palm
32. Onion
33. Orange
34. Peas
35. Peanut
36. Peppermint
37. Pistachio
38. Pomegranate
39. Psyllium
40. Pumpkin
41. Roselle
42. Sage
43. Sesame
44. Soy
45. Tamarind
46. Tulsi
47. Turmeric
48. Walnut
49. Watercress
50. Wasabi.

The FDA would probably prosecute me if I were to prescribe them for lowering bad cholesterol, much less suggest the fact that herbistatins might be as helpful in AD as the synthetic statins. A 22 January 2016 PubMed search on "Statins AND Alzheimer's AND Clinical" yielded 253 results. The most recent citation was a Cochrane Review that concluded, "There is good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia" (PMID 26727124). I hope, but do not know, that Cochrane reviews average more trustworthy than most PubMed scientific articles. Some statin critics suggest that statins may worsen AD, and that's what my bias says. But who are we to believe?

In the second citation, the title asks, "Are statins protective or harmful to cognitive function?" The author concludes: "In February 2012, the FDA issued safety label changes and monitoring requirements for statin therapy. A risk of cognitive impairment was noted, although evidence was largely based on observational data, including case reports. In 2014, the National Lipid Association's safety task force found that evidence does not support cognitive decline as a class-wide effect for statins. Some evidence has shown that statins may actually have beneficial effects on cognition" (PMID 26704648). I would expect that the National Lipid Association would challenge such negativity about synthetic statins. I was pleased, however, to

Hibiscus sabdariffa
(roselle, sorrel) calyxes

see that, by 2012, the FDA called attention to the possibility of statins causing AD.

In the third citation, seven Chinese scientists seem skeptical: "It has been well identified that CSVD [cerebral small vessel disease] contributes to the occurrence of AD. It seems that the treatment and prevention for cerebrovascular diseases with statins [would] have such a role in the same function for AD. So far, there is no strong evidence-based medicine to support the idea, although increasing basic studies supported the fact that the treatment and prevention for cerebrovascular diseases will benefit AD. Furthermore, there is still lack of evidence in clinical application involved in specific drugs to benefit both AD and CSVD" (PMID 26604717).

Another inquisitive review from 2015, "Statins for Treating Alzheimer's Disease: Truly Ineffective?" states: "Four studies (1,127 participants) involving patients with a diagnosis of probable or possible AD were included. There were no significant differences between the statins and placebo groups regarding the main outcomes, secondary outcomes, or adverse events. Most of the studies ignored or downplayed risk factors for cerebral vascular disease" (PMID 26021802).

I'm not even going to read the remainder of the 253 PMID abstracts, much less the entire papers. I'm of the entrenched opinion that natural herbistatins will be safer than synthetic statins and will contain a greater diversity of anti-AD phytochemicals. Many, not all, allopaths and nutritionists prefer to work with isolated phytochemicals to better control dosage. Many, not all, herbalists and naturopaths prefer to work with whole natural organic herbs rather than the isolated phytochemical out of context.

Sources and Activity of Herbistatin Phytochemicals

Herbistatic Phytochemicals	Source(s)	Activity (Experimental dose)	PubMed Citation(s)
Betaine	Beets, Cacti, *Centrospermae*	HDL-genic	22577451, 22442957
Biochanin-A	Legumes	HDL-genic (50 mg/kg orl rbt)	1800305
Choline	Widespread	HDL-genic	22577451
Cinnamaldehyde	Cinnamon	HDL-genic	17140783
Cinnamates	Cinnamon	HDL-Genic	14585184
Beta-Conglycinin (Soybean Fraction 7S)	Soy	HDL-Genic	21138348
Costunolide	Crepe Ginger, Lettuce, Chicory	HDL-genic (500 mg/day for one week)	19007766
Curcumin	Turmeric	HDL-Genic	1291482
3,5-Dihydroxy- phenylpropionic Acid (DHPPA)	Whole grains	HDL-Genic	20553191
Diosgenin	Fenugreek, Wild Yam	HDL-Genic	208586, 438658, 21902054
Epicatechin	Green Tea, Cocoa, Prunes	HDL-Genic (50-100 mg orl hmn)	22735710
Episesamin	Sesame	HDL-Genic	9072406, 9072406
Eremanthin	*Costus*	HDL-Genic (20 mg/kg/day)	19695236, 20709041
Ferulic Acid	Widespread	HDL-Genic	20553191, 20553191
Flavonoids	Ubiquitous	HDL-Genic	18593176
Glycinin	Soy	HDL-Genic	21936891
Glycyrrhizic Acid	Licorice	HDL-Genic	20670429
Gymnemate	*Gymnema*	HDL-Genic	1669131
Hesperetin	*Citrus*	HDL-Genic	18593176
4-Hydroxyisoleucine	Fenugreek	HDL-Genic	18680121, 22397995
Magnesium	All Plants	HDL-Genic	15466951
Mogrosides	*Siraitia*	HDL-Genic	19083420
Niacin	Rather ubiquitous	HDL-Genic	19915217, 22085343
Oleuropein	Fringe Tree, Olive	HDL-Genic	18823963
Gamma-Oryzamol	Rice	HDL-Genic	11406848
Pinitol	Carob, Soy	HDL-Genic	15536472, 18752266 19205001
Piperine	Black Pepper	HDL-Genic	16910313
Piperlongumine	Long Pepper	HDL-Genic	18533506
Pterostilbene	Grape, Almonds, Blueberries, Malabar Kino	HDL-Genic	15853379
Quercetin	Ubiquitous	HDL-Genic (100 mg/day)	18823963
Resveratrol	Grape, Mexican Bamboo, Peanut	HDL-Genic	18611391, 22465220
Sesamin	Sesame	HDL-Genic	9072406
Tetrahydrocannabinol	Hemp	HDL-Genic	15776349
Tocotrienols	Rice bran oil, Palm oil, Saw palmetto berry	HDL-Genic	21702918, 21774782